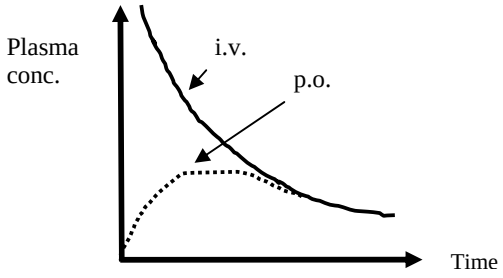
Exam in BB2170 Drug Development
Friday March 19th, 2010, at 14-18

Total: 50 points
Pass: 25 points

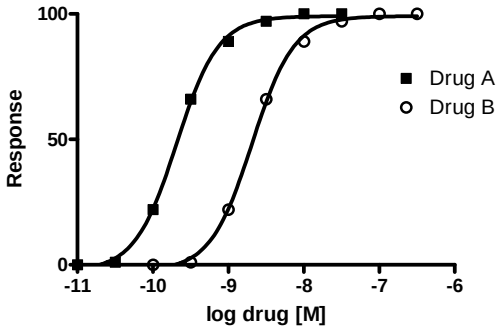
Part I. Answer the following questions; short answers:

1. What are the distinguishing features of 1st order and 0th order kinetics? (2 p)

2. Below you see a plot of the plasma concentration curves after per oral (p.o.) and intravenous (i.v.) administration of a drug. How do you calculate the bioavailability of the orally administered drug from this information? (2 p)



3. Drug A and Drug B were both tested in an *in vitro* pharmacological assay at a series of different drug concentrations, resulting in the dose-response curves shown below. How do you calculate the EC50 from these curves? Based on this experiment, which drug candidate appears to be the most efficacious? Discuss why does-response curves are better for the evaluation of new compounds, compared to testing the compounds at single concentrations. (3 p)



4. Elderly are commonly prescribed many drugs and also use over the counter supplements. Why is this important to consider when developing a drug? (1 p)

5. Explain the concept of allometric scaling for the prediction of pharmacokinetic parameters. (2 p)

6. Some of the cytochrome P450 enzyme isoforms involved in drug metabolism are characterized by genetic polymorphism. Explain what genetic polymorphism means, and its relevance for the therapeutic use of the drugs. (2 p)

7. Describe briefly how cationic polymers can be used for delivery of drug compounds into a cell. (2 p)

8. The process development is important for the production of biopharmaceuticals. Give a brief description of what can be optimized to improve the process in the a) Upstream process development, and b) Downstream process development. (3 p)

9. A common method for engineering a biopharmaceutical is the covalent coupling of polyethylene glycol (PEG) polymer chains to the protein. What are the advantageous effects of pegylation of a protein? Give at least two examples. (2 p)

10. For a new drug, the beneficial effects have to be compared to the side effects. What criteria are considered in the risk-benefit analysis? (3 p)

11. How could the crystal structure of a potential new drug target be of help in the drug discovery/development process? (2 p)

12. In recent years, more attention has been turned to the environmental aspects of the production of pharmaceutical drugs. How can the principles of “green chemistry” be applied to the organic synthesis of a drug compound? Give at least two examples of factors to consider for reduction of the environmental impact of a manufacturing process. (2 p)

Part II. Answer the following questions; more detailed answers.

13. For a pharmaceutical company there are two major strategies for developing a new drug for a certain indication: (i) identification of an entirely new target, or (ii) starting with a known target for which there is already a drug on the market. Discuss possible advantages and disadvantages of the two approaches. Describe the methods used in the pharmaceutical industry to generate and validate new drug targets. (6 p)

14. Imagine that you are a medicinal chemist at a pharmaceutical company. After a high throughput screening campaign against a new target, 100 confirmed hits have been identified. Your job is to pick out 5 of the 100 compounds to go forward with in a lead optimization process. Discuss what considerations you make when choosing the five compounds. (6 p)

15. Antibody-drug conjugates have recently gained much attention and have been described as “a marriage of biologics and small molecules”. Discuss the respective roles of the antibody and the small molecule in such a pharmaceutical and compare the strategy to using either type of compound alone. Discuss how antibody conjugates could be used in cancer therapy and describe the mechanisms of action for at least three examples of payload that can be conjugated to antibodies. (6 p)

16. Applying for and maintaining a patent is very costly process. What rights does the protection give the owner of the patent? How can this investment be used to make money in return for the company? Discuss how different patent strategies can be used in a pharmaceutical or a biotech company. (6 p)

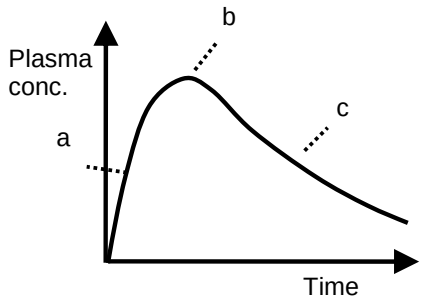
Exam in BB2170 Drug Development
Monday June 7th, 2010, at 14-18

Total: 50 points
Pass: 25 points

Part I. Answer the following questions; short answers:

1. Give three examples of factors that can affect the absorption of a drug. (3 p)

2. A plasma concentration curve is shown below. What are the phases a, b and c after per oral administration of a drug called? Describe briefly what happens to the drug during each phase. (3 p)



3. Make a figure sowing the dose-response curves for: (3 p)

a) a full agonist
b) a partial agonist
c) a partial agonist in the presence of a constant concentration of a full agonist

4. What is a prodrug? (2 p)

5. Biopharmaceuticals, such as monoclonal antibodies, are typically produced in host organisms. The purity of the final product is very important and much effort is devoted to the downstream processing and quality control. Give at least two examples of possible host cell contaminants and describe how the final product is analyzed to assess the purity. (2 p)

6. Explain briefly how transgenic mice can be used as disease models in the drug discovery process. (2 p)

7. The liver metabolism typically occurs in two steps: the phase I reactions and phase II reactions. Describe briefly the two types of reactions. (2 p)

8. What property of a drug compound is measured in the Caco-2 cell assay? (1 p)

9. The concept of personalized medicine has gained more attention with the recent improved possibilities for genetic testing and proteomic profiling of patients. What is personalized medicine, and how could it be used in the clinic? (1 p)

10. What is the Ligand Efficiency (LE) and what is the purpose of calculating LE indices for a compound? (2 p)

11. What types of formulations are used for oral administration of drugs? Give at least two examples. (2 p)

12. Discuss briefly the different criteria for patentability. (3 p)

Part II. Answer the following questions; more detailed answers.

13. In the pharmaceutical industry two main strategies are used for the screening of compound libraries: high-throughput screening of large, non-biased libraries and low-throughput screening of smaller, focused libraries. Describe the two approaches and discuss what you think is the best strategy to use for the development of a new drug. (6 p)

14. The costs associated with the development of new drugs are known to increase when entering into clinical trials. Discuss a) why the clinical trials are expensive, b) what the main reasons for failure of candidate drugs in the clinical trials are, and c) what strategies the pharmaceutical industry is using to identify potential shortcomings of a compound before going into the clinical trials. (6 p)

15. Monoclonal antibodies are becoming an increasingly important class of drugs. Since the first mouse monoclonal antibody was approved for therapeutic use in 1986, different types of engineered antibodies have been developed: a) chimeric antibodies, b) humanized CDR-grafted antibodies, c) phage display-generated human antibodies, and d) human antibodies generated from transgenic mice.
What was the main issue concerned with the use of mouse monoclonal antibodies, that stimulated the development of new antibody variants? What are the distinguishing features of the four types of engineered antibodies mentioned above? Discuss briefly the potential advantages of each of the different strategies. (6 p)

16. The majority of all drugs in use today are targeted towards proteins and in the generation of new drug targets, it is important to establish a link between the disease and the potential target protein. Discuss how expression studies (on protein and/or mRNA level) can be used to identify new drug targets. Which protein classes are the most popular drug targets today? (6 p)

Exam in BB2170 Drug Development
Tuesday March 15th, 2011, at 14-18

Total: 50 points
Pass: 25 points

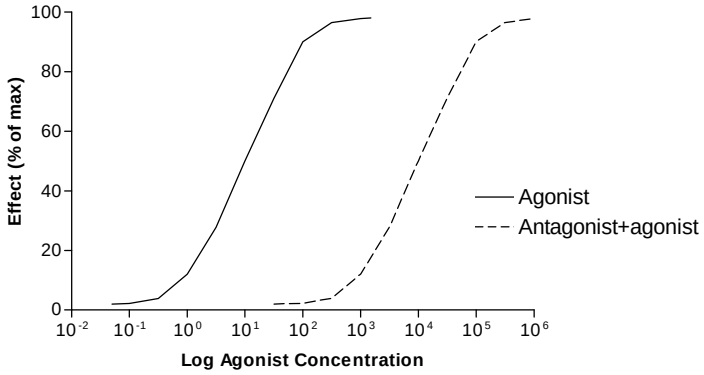
Part I. Answer the following questions; short answers:

1. The passage of a drug across a plasma membrane can occur by three main different mechanisms. What are the mechanisms, and how do they differ? Which mechanism is the most common for drugs? (3 p)

2. What is clearance, CL, and how is it calculated for 1st order kinetics? (2 p)

3. What is a "loading dose"? What is the purpose of giving a loading dose? (2 p)

4. The graph below shows the effect of different concentrations of an agonist on the contractility of a blood vessel in an organ bath. The experiment is repeated, but this time an unknown antagonist is added first. What kind of antagonist is added? Explain! (2 p)



5. Drug-drug interactions can affect the plasma concentration of an administered drug. Describe briefly at least two examples of possible mechanisms for this effect. (3 p)

6. The administration of protein pharmaceuticals is a challenging task. Describe the problems associated with this class of compounds, and potential solutions. (2 p)

7. A general problem when doctors prescribe drugs to patients is the low compliance, i.e. that the patient is not taking the prescribed drug at the intended dose or time interval. How can the compliance possibly be improved by the formulation of the drug? Give at least two examples of strategies that are used. (2 p)

8. What is the difference between a "hit" and a "lead"? Explain briefly! (2 p)

9. The majority of all drugs in use today are targeted towards a protein. Which protein classes are the most common drug targets? (2 p)

10. What is a generic drug? (1 p)

11. What is the “inventive step” in the context of a patent application, and how can it be questioned? (2 p)

12. Describe briefly the main goals of phase I, phase II and phase III of the clinical trials. (3 p)

Part II. Answer the following questions; more detailed answers.

13. When testing new compounds, the screening assay can be very complex (and even involve testing in living animals, as in the development of the drug “Losec”) or be a very simple, biochemical assay. a) Discuss advantages and disadvantages of complex versus simple screening assays. b) Why is the robustness of a screening assay critical and how can it be assessed? (6 p)

14. Protein engineering provides many opportunities for improving the properties of antibodies as pharmaceuticals. Discuss possible strategies and give at least one example of how engineering of a monoclonal antibody generated in mouse can be used to:

a) reduce the immunogenicity
b) improve the antigen-binding affinity
c) decrease the molecular size (6 p)

15. Animal models are frequently used both in the early drug discovery phase and in the preclinical drug development phase. Discuss what kinds of studies are performed in animals, and possible reasons of drug failure that are related to the use of animal models. (6 p)

16. When scaling up the production of a new drug, different factors have to be considered. Describe important considerations when scaling up production processes for a) small-molecule drugs, and b) protein drugs. (6 p)

Exam in BB2170 Drug Development
Wednesday June 8th, 2011, at 14-18

Total: 50 points
Pass: 25 points

Part I. Answer the following questions; short answers:

1. What is the difference between systemic and local administration? Give an example of an administration route for each class. (3p)

2. Explain how the pKa of a drug can affect its absorption and distribution in the body after administration to the patient. (2 p)

3. How is the distribution volume (Vd) calculated? (1 p)

4. What are a competitive antagonist and a non-competitive antagonist? (2 p)

5. What is affinity? (1 p)

6. For a new drug candidate side effects are an important issue. What types of methods are used for the risk assessment? (3 p)

7. What is NOAEL and how is this concept used in drug development? (2 p)

8. Explain the concepts “Poor metabolizers” and “Extensive metabolizers” in the context of drug metabolism. Why is it particularly important to study the metabolism of a drug if it has a narrow therapeutic interval? (3 p)

9. Two important classes of protein therapeutics are replacement (or substitution) therapeutics, and targeting proteins (often monoclonal antibodies and derivatives thereof). Describe briefly the two classes of drugs and give an example of a disease that can be treated with each class of substance. (3 p)

10. Drug development is a strictly regulated business area. Why? Discuss possible reasons for the authorities’ strict regulations. (2 p)

11. Explain the terms “First medical indication” and “Second medical indication” in drug patent applications. (2 p)

12. Give two examples of how a synthetic route can be improved to make the production process more cost efficient and environmentally friendly. (2 p)

Part II. Answer the following questions; more detailed answers.

13. For the medicinal chemist there are a number of desirable features in a project aiming at the development of a new small-molecule drug. Discuss why the following features could be considered advantageous:

- The target is extracellular (instead of intracellular)
- The target is peripheral (instead of central)
- The X-ray structure is known (6 p)

14. Give three examples of so-called intrinsic effector functions present in antibody therapeutics and briefly describe the mechanism of action for each type. (6 p)

15. When the patent expires for a blockbuster drug there is likely to be competition from other companies selling the same substance at a lower price. Discuss why biopharmaceuticals are much more difficult to copy than small-molecule drugs. (6 p)

16. Many new drug candidates fail when tested in human during the clinical trials. Describe the studies performed during each phase of the clinical trials and give examples of possible reasons for failure during the different phases. (6 p)

Exam in BB2170 Drug Development
Wednesday December 14th, 2011, at 9:00-13:00

Total: 50 points
Pass: 25 points

Part I. Answer the following questions; short answers:

1. Give three examples of factors that can affect the absorption of a drug. (3 p)

2. What is bioavailability? Explain briefly. (2 p)

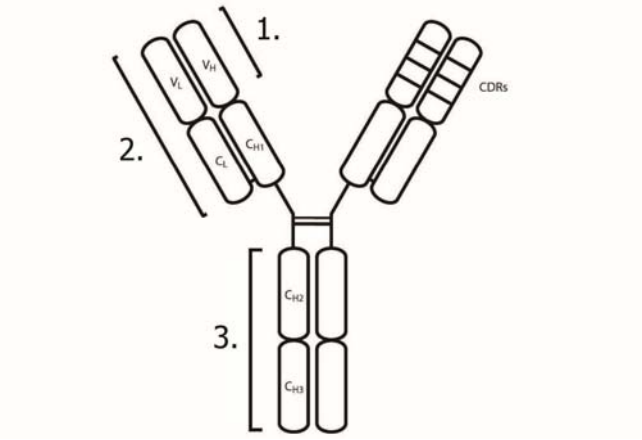
3. Making dose-response curves is important for the evaluation of new compounds. Draw a dose-response curve for a partial agonist and explain how the *efficacy* and the *potency* of the compound can be determined from the graph. (3 p)

4. The liver metabolism typically occurs in two steps: phase I reactions and phase II reactions. Describe briefly the two types of reactions performed by the metabolic enzymes. (2 p)

5. Explain briefly how transgenic mice can be used as disease models during the drug discovery process. (2 p)

6. When scaling up the synthesis of small molecule drugs for production purposes, both economic and environmental factors need to be considered. Describe why catalysis can be an attractive feature of a synthesis process when considering such factors. (2p)

7. The figure below is a schematic drawing of an IgG molecule. What are the parts (1), (2) and (3) called? Which part of the antibody is necessary for the ADCC and CDC mechanisms in antibody therapy? (3 p)



8. Chemical and physical degradation can lead to heterogeneity and reduce the activity of a protein drug. Give at least three examples of such protein modifications. (2 p)

9. *Life cycle management* is an important concept in the pharmaceutical industry, which aims at maximizing a drug's profits during its commercial life. Give two examples of strategies that can be used by a pharmaceutical company to continue earning money from a developed drug after the original patent expires. (2 p)

10. In modern pharmaceutical industry an important activity is the *innovation management.* On what three levels can innovation be managed? Describe briefly. (2 p)

11. A mile-stone in the development of a new drug is the first-in-man study performed in a small number of healthy volunteers during the phase I clinical trials. Describe briefly what is assessed in this study and what results are needed to proceed to phase II. (3 p)

Part II. Answer the following questions; essay-type answers:

12. A common way to describe the drug discovery process is to divide it into four stages: Target Identification (TI), Hit Identification (HI), Lead Identification (LI) and Lead Optimization (LO). Describe typical activities during the different stages and the deliverables of each step. (6 p)

13. Company A is developing a new drug for treating high blood pressure, which affects millions of people world-wide. Company B is developing a new drug for a rare genetic disease, with a total of one thousand patients world-wide, for which there is not available treatment on the market. Discuss the strategic considerations made by the two companies and give reasons for choosing each of the two approaches. (6 p)

14. Toxicological testing of new drug candidates in animals is an important step of the drug development process. Discuss general differences between small-molecule drugs and protein drugs that have implications for the toxicity of the two drug classes. (6 p)

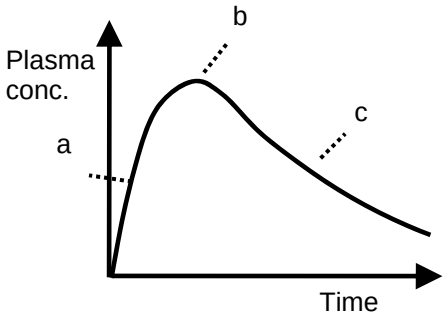
15. Applying for and maintaining a patent is very costly process. What rights does the protection give the owner of the patent? How can this investment be used to make money in return for the company? Discuss how different patent strategies can be used in a pharmaceutical or biotech company. (6 p)

Exam in BB2170 Drug Development
Monday January 9th, 2012, at 9:00-13:00

Total: 50 points
Pass: 25 points

Part I. Answer the following questions; short answers:

1. A plasma concentration curve is shown below. What are the phases a, b and c after per oral administration of a drug called? Describe briefly what happens to the drug during each phase. (3 p)



2. What is first-pass metabolism? Explain briefly. (2 p)

3. Most drugs are eliminated by first-order kinetics at therapeutic doses. Explain the main differences between first-order and zero-order kinetics, and explain why the elimination can shift from first-order to zero-order at high doses. (3 p)

4. What is EC50 and how can it be determined from a dose-response curve? (2 p)

5. Describe briefly two strategies that can be used to identify a new drug target for a disease. (2 p)

6. The synthesis of compounds containing stereogenic (chiral) centres can be a challenge for the synthetic chemists. Give two examples of possible sources for chirality in pharmaceutical compounds. (2 p)

7. What is PEGylation? How can it be used to improve a protein drug? (2 p)

8. The concept of *Green Chemistry* is becoming increasingly important for the synthesis of drug compounds. Choose three out of the twelve principles of green chemistry and for each principle describe briefly its relevance for process synthesis. (3 p)

9. An ideal drug should not show any induction or inhibition of metabolic enzymes. Why? (2 p)

10. What does the concept of dominant design stand for in the field of innovation management and technological evolution? Describe how the concept can be transferred in order to describe the current process for pharmaceutical innovation. (2 p)

11. What is NOAEL? When NOAEL has been determined in animal, an assessment factor is used to determine the recommended starting dose for the first-in-human clinical trial. Describe why an assessment factor is used to calculate the dose. (3 p)

Part II. Answer the following questions; essay-type answers:

12. When building a compound collection for screening, the theoretical number of possible chemical structures is almost infinite, but in practice both the time and resources limit the number of substances that can be synthesized. Discuss how computational chemistry and prior knowledge can be used as tools when designing a compound collection. (6 p)

13. In principle, a screening assay is equivalent to a laboratory experiment where the effect of a compound on a biological system is measured. However, for the development of an assay suitable for High Throughput Screening (HTS), a number of considerations have to be made. Discuss what properties an ideal HTS assay should have, and what should be avoided. (6 p)

14. One of the concerns in the development of a new drug is the safety assessment. Explain how the safety of a drug candidate is studied during a) the preclinical studies and b) during Phase I of the clinical studies? (6 p)

15. Monoclonal antibodies are becoming an increasingly important class of drugs. In addition to traditional mouse monoclonal antibodies, different types of engineered antibodies have been developed, for example: 1) humanized antibodies, 2) phage display-generated human antibodies, and 3) human antibodies generated from transgenic mice.

Describe the three types of engineered antibodies mentioned above and discuss briefly the potential advantages of each of the different strategies for the generation of therapeutic antibodies. (6 p)

Course BB2170 – Drug Development – KTH – Examination date 2015-01-19

A. Questions (answered by brief answers)

1. The clinical trials before drug registration are

clinical trial phase I,

clinical trial phase IIa and clinical phase IIb,

clinical trial phase III.

a) For each of these clinical trials, what are the objectives of the trials?

b) For each of these clinical trials, which subjects are enrolled for the clinical trials? (2p)

2. Nanoparticles (NPs) can be used for drug delivery. Different types of NPs are available and can have different properties or characteristics. Give at least 3 properties (or characteristics) of NPs in drug delivery and a brief explanation or example of each property (or characteristic). (2p)

3. What are a) clearance, b) volume of distribution, c) bioavailability and d) half-life of a drug? How can pharmacokinetics information of clearance, volume of distribution, bioavailability and half-life be predicted for human during preclinical development? (2p)

4. Below are two affirmations about patenting, for each one, write if it is correct or not and justify your answer.

a) Mister Hu has developed a new method to purify proteins from plant extract in view of producing a drug medicine. He has presented this method in an agriculture school in Xian (in China). Mister Hu can patent this method in Europe and USA but not in China because it was presented in China. (1p)

b) Madam Smith has created a new molecule helping to treat headache and has patented her invention. During the phase II clinical trial, it is shown that this new molecule is not an improvement compared to existing drugs, i.e. the effect of the drug is comparable to other existing drugs but is not an improvement. A competitor can therefore attack this patent and make it not valid. (1p)

5. Explain the concepts “Poor metabolizers” and “Extensive metabolizers” in the context of drug metabolism. Why are certain subjects poor metabolizers and certain subjects extensive metabolizers? Explain shortly why it is particularly important to study the metabolism of a drug if the drug has a narrow therapeutic interval? (3 p)

6.

a) Explain the concept of “humanized” antibodies and explain why these types of engineered antibodies are normally preferred over mouse antibodies for clinical use in humans.

b) Explain the concept of “chimeric” antibodies.

c) Give three examples of how fully human antibodies can be generated. (3p)

7. Give (at least) two important factors (or components) for the formulation of protein drugs. Give (at least) two stability problems observed in the formulation of protein drugs. (2 p)

8. What is fragment screening for hit identification? What is the advantage of fragment screening for hit identification compared to screening using larger molecules (HTS)? (2 p)

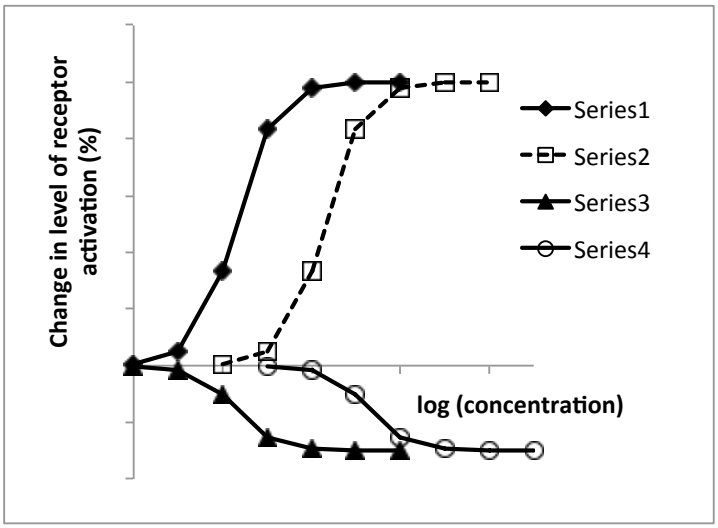
9. In the graph below, Series 1 (continuous line, closed diamond symbols) shows the effect of different concentrations of an agonist A on the contractility of a blood vessel in an organ bath.

The experiment is repeated in presence of compounds A and B and curve 'Series 2' (dotted line, open square symbols) is obtained. What kind of compound is B and what kind of action does compound B in presence of compound A?

The experiment is repeated with the new compound C, and curve 'Series 3' (continuous line, closed triangle symbols) is obtained. What kind of compound is C and what kind of action does compound C?

The experiment is repeated in presence of compounds C and D, and curve 'Series 4' (continuous line, open circle symbols) is obtained. What kind of compound is D what kind of action does compound D in presence of compound C?

(3 p)



10. Nowadays many scientists are looking at novel biopharmaceuticals based on antibodies (MAb), where the properties of the antibodies are associated with another kind of effect by modifying, engineering or complementing the antibody with this other effect or where the native form of the antibody is changed to increase or modify the therapeutic effect(s). Describe 3 novel biopharmaceuticals and their working principle. (3p)

B. Questions requiring an assay-type answer, i.e. a longer answer, where you show a deeper knowledge and can analyse or reflect on the subject

11. Drugs can be divided into two groups: small molecule drugs and protein drugs (or biopharmaceuticals). For new registered drugs, which group used to be the most represented in the past i.e. before 1985? The distribution of new registered drugs between small molecules and proteins has changed since 1985 and nowadays. How is the actual distribution for new registered drugs between small molecules and proteins? Describe what has happened between 1985 and nowadays and discuss the reasons for the evolution of this distribution (i.e. what have been/are the factors, which have caused/are causing higher or lower success rate in the development of new drugs in each categories. Think as well for your argumentation that there are different types of biopharmaceuticals). (6p)

12. Imagine that you are a medicinal chemist at a pharmaceutical company. After a high throughput screening campaign against a new target, 100 confirmed hits have been identified. Your job is to pick out 5 of the 100 compounds to go forward with in a lead optimization process. Discuss what considerations you make when choosing the five compounds. (6 p)

13. When their patents have expired, the existing drugs are often copied and commercialized by other companies as generic drugs for small molecule drugs and as biosimilars for biopharmaceuticals. Discuss the development of biosimilars versus small molecule generic drugs: What is the easiest to develop and why? Motivate your answer. Is it necessary to do clinical trials for a new small molecule generic? Motivate your answer. Is it necessary to do clinical trials for a new biosimilar biopharmaceutical? Motivate your answer. (6 p)

14. Animal models are frequently used both in the early drug discovery phase and in the preclinical drug development phase. Discuss what kinds of studies are performed in animals. What are the possible reasons of drug failure that are related to the use of animal models? How (and in which purposes) can transgenic animals be used as disease models? (6 p)

ANSWERS

1. Objectives:

clinical trial phase I: **pharmacokinetics** (describe/define PK and PD, food effect, drug metab, interaction studies), dose estimation, **safety** (assess safety and tolerability)

clinical trial phase II: **dose ranges**, **safety** in **diseased** people, pharmacological activity, interactions. In particular clinical trial phase IIa: to document the effects in humans, **proof-of-concept** and clinical phase IIb: to document the **lowest efficacious** does, dose-finding, show efficacy in patients over longer period with different doses

clinical trial phase III: **benefit analysis**, safety, efficacy, data for MAA, **larger population**

Subjects:

clinical trial phase I: **healthy** volunteers, closely controlled

clinical trial phase IIa and clinical phase IIb: target **disease**, strict inclusion/exclusion criteria, **small groups**

clinical trial phase III: **broad & representative population, larger groups**, specific sub-groups

2.

- Different types: liposomes, polymer micelles, dendrimers, gold NP, nanotubes, nanocrystals
- Improved bioavailability /extremely small size /high surface area: nanocrystals are of much smaller size, have an increased bioavailability, improved rate of absorption
- Passage of biological barriers: ex. NP can have properties such that they can pass the BBB
- Target delivery: ex. tumor have a lower pH. NP's can circulate in the body and, when coming to the tumor (=target), release their active component in response to the lower pH environment
- Multifunctional NP/possibility to use NP for treatment and diagnostic (theranostic): diagnostic agents (gold particles, fluorescent dyes, etc) can be integrated in the same NP as the therapeutic agent (e.g. protein) so that info of effect (e.g. distribution, imaging) can be followed when drug is administrated
- Controlled release: ex. a drug is administrated in NP, then by effect of heat or light, the drug is locally released at its target
- Intake via endocytosis of NP followed by drug release, enhanced permeability
- Increase of stability: ex. liposomes can prolong the circulation time in the blood
- Reduced toxicity: ex. liposomes can reduce the cardiotoxicity

- Delivery of poorly soluble drug: ex. using albumin as a natural carrier Paclitaxel, which is poorly soluble, can be delivered using albumin transport pathway. This confers also reduced side-effects.
- Administration via different routes
- Polymeric micelles of PEG

3. Clearance: animal data using allometric scaling and/or in vitro data for human system simulation, where allometric scalling is based on different animal data with extrapolation to human based on body weight. Volume of distribution: allometric scaling. Bioavailability: human simulation system using in vitro data (caco-2 cell line), animal data and in vitro vs. in vivo comparison. Half-life: using information of predicted volume of distribution and clearance.

Clearance = volume that is totally cleared from drug every time unit.

Volume of distribution = apparent volume of fluid containing the drug in the body

Bioavailability = fraction of drug that enters the central systemic circulation upon administration via the chosen therapeutic route.

Half-life = half the time length that the drug stays in the body

4.

a) Mister Hu's patent will not be allowed because it has been published. The geographical location of where it was disclosed (China) has no importance.

b) Madame Smith will keep her patent given that the molecule is new. (However she might not been able to file her new drug for clinical study III due to the lack of improvement compared to existing drugs but this is not relevant for the patentability)

5. PM and EM: cytochrome P450 isoforms with low and high activity, respectively. If the drug is metabolized by isoformic enzymes the blood concentration after administration will vary between different individuals with a high risk of going outside the therapeutic interval.

6. Chimeric: mouse V domains, human C domains.

Humanized: mouse CDRs, the rest of the mAb is human

Immune response to the mouse antibody protein, which is considered foreign, leads to the production of neutralizing antibodies and other possible side effects.

Human antibodies can be generated by phage display, transgenic mice with human immune system.

7. pH, stabilizer, solubiliser, buffer, tonicity modifier/bulking agents.

aggregation, deamination, cleavage, oxidation, surface denaturation

8. A: The active site of a target is typically constituted of several pockets. 'Fragments' are molecules of size ≤ 250 Da with high affinity with one of these pockets but resulting in a low affinity with the whole active site. By combining several of these fragments with affinity to different pockets, a resulting molecule can be a better potential lead with a final higher affinity, lower molecular size, easier synthesis, better solubility, than obtained by HTS screening of larger molecules. Furthermore, compared to HTS, fragment screening is using smaller component libraries.

9. B = competitive antagonist. The antagonist competes with the agonist by binding to the same receptor. In presence of the antagonist, a higher amount of agonist is necessary to obtain the same effect.

C = inverse agonist. It binds to the same receptor as the agonist but induces an effect opposite to the agonist.

D = competitive antagonist. The antagonist competes with the inverse agonist. In presence of the antagonist, a higher amount of inverse agonist is necessary to obtain the same effect.

10. Alternative ways: 1) Use of Fab instead of full length antibody can be as active as the full-length antibody while requiring lower production cost - for instance because it can be produced in E. coli instead of mammalian cell, fragment of Ab have shorter half-life, which might be a disadvantage but can also be desirable in some cases. 2) Small bi-specific antibody have been developed $(svFv)_2$, these recognize an immune cell and the target cell simultaneously so that the immune cell can destroy the pathogenic cell; the advantage compared to MAb is that a MAb would recognize only one of these cells. 3) Antibody conjugate protein where for instance an antibody is linked to a toxic molecule; after the recognition of the antibody for the target cell and internalisation, the toxic component does its lethal action killing the target cell; the advantage compared to the MAb alone is a more effective way to kill a target cell. 4) Bi-specific antibodies can be composed of a chimeric antibody including different Fab (instead of 2 identical Fab's) with affinity for different antigens, or one Fab can be designed to recognise 2 antigens; this allows binding different antigens and have a double action compared to the single action of the MAb. 5) Polyclonal antibody or combination therapy including several MAb allow to treat with several types of antibodies simultaneously, which can be an advantage when the illness can be attacked by several pathways simultaneously or in case of polymorphism of the disease.

11. In 1985, the new NMEs were in ***majority small molecules*** while nowadays it is about 50/50 between small and protein drugs. Protein drugs came around 1980, first with the ones produced by micro-organisms and then a bit less than a decade later accompanied by the ones produced by mammalian cells. The first protein drugs were mostly replacement proteins to restore lacking functions in the body. Progressively appeared other types of effects, largely represented by

the antibodies and related molecules. Today the success of biologics is largely due ***antibody*** and antibody-based molecules. Protein drugs have a lower attrition rate compared to small molecule drugs. The progresses in ***biologics process development*** have been immense, with today very high production levels in mammalian cells enabling complex biopharmaceutical production. A general trend is that the low hanging fruits have been picked so the new drugs require today more efforts for their creation and for their registration. The authorities have increased their requirements and are asking for a better understanding of the underlying mechanism and a higher safety for the new NMEs compared to the past requirements. With years, the orphan drugs have attracted more investment and can be today very profitable. There a series of replacement molecules are obvious candidate drugs. The market has changed as well, from a stage where only the blockbusters were interesting several years ago to a situation today where smaller drug are also interesting; favouring drugs with smaller number of patients (but much more expansive). The success of developing ***new small molecule drugs has been low*** lately despite increasing efforts in resources and improved methods (large efforts based on HTS has not been so fruitful as expected). It has become clear recently that missing factors for drug development have been lack of using biomarkers during the whole drug development process and lack of fundamental/mechanistic understanding of the target diseases. Compared to small molecules, biopharmaceuticals can often be delivered at their site of action by ***affinity, with specificity, which reduces the risk of side effects*** observed with the small molec delivered in the whole body. The number of new drug proteins and small molecule drugs has been close to 50/50 distribution since 1996 and it is probable that this even distribution will continue in the near future.

12. Considerations:

1. Choose five independent substance classes
2. Affinity for the target
3. Pharmacological efficacy/potency
4. Cost-efficient synthesis
5. IP issues

ADME properties:

1. Stability
2. Lack of early toxicity/reactive groups
3. Lipinski score
- MW,
- HBD/HBA,
- permeability
4. Ligand efficiency (higher MW typically gives higher affinity but lower solubility and increased metabolism)

13. Small molecule generics are easier to develop since their formula is unique. Biosimilars are large molecules (most often proteins) and are defined not only

by their formula but also by the profile of the drug defined by its specifications (set of analyses looking at different aspects of the drug, i.e. process related impurities, product related impurities), and very importantly by the production process (including many different steps/factors of variations such as the cell host and clone, culture process, medium/-ia, purification process, …). For generics: no clinical trials, for biosimilars: yes: clinical trials. Since generics can be exactly copied, the patient will receive exactly the same molecule. In the case of biosimilars, it is impossible to have exactly the same molecule as the original drug, so the effects of this biosimilar have to be studied/confirmed in clinical trials.

14. Animal disease models: for target identification and target validation, screening, and safety assessment in preclinical drug development phase.

Safety assessment: testing in animals, typically two species.

Advantage: Intact organism gives an overall view of the toxicity and good prediction of human toxicity and drug efficacy.

Qualitative and quantitative differences between animals and humans are seen. Differences in ADME/PK/PD and physiological differences can give false positives (e.g. different metabolism) and false negatives.

Transgenic mice overexpressing a certain gene to mimic a disease condition and/or knock-out of a target gene: understanding of disease mechanisms, testing of effect of a new drug.

Course BB2170 – Drug Development – KTH – Examination date 2016-10-25

There are 2 types of questions: A (with 9 questions for a total of 160 points) and B (3 questions for a total of 160 points). **All** the **12** questions have to be answered.

Use only one side of paper.

Either only one or several questions can be answered on one paper sheet.

A. Questions (answered by brief answers)

1.

1.a During the absorption phase, a small molecule drug delivered orally is taken up from the intestine to the body. Give at least 4 factors that influence the absorption of a small molecule drug to the body. For each factor, briefly describe how the factor influences the drug absorption.

1.b. The drug is then differently distributed in the diverse parts of the body. Give at least 4 factors that influence the distribution of a small molecule drug in the different body parts. For each factor, briefly describe how the factor influences the drug distribution. (30 p)

2. Different ways (or techniques or approaches) are used in Target generation. Give at least 3 ways to generate and/or validate targets used for drug development; and give a brief description of what these ways are. (15 p)

3. One of the concerns in the development of a new drug is the safety assessment. Explain briefly how the safety of a drug candidate is studied in a) the preclinical studies and b) in phase I of the clinical studies? (20 p)

4. In recent years, more attention has been put on the environmental aspects of the production of pharmaceutical drugs (i.e. small molecule drugs). How can the principles of “green chemistry” be applied to the organic synthesis of a drug compound? Give at least five factors to consider for reduction of the environmental impact of a manufacturing process. (10 p)

5. Venture capitalists (VCs) are important when starting-up a new pharmaceutical/ biopharmaceutical company. Give at least three supports that VCs provide in the start-up phase? (15 p)

6. For a pharmaceutical company, it is very important to have patents to protect new inventions. However to wait before patenting can also be advantageous (i.e. to patent a little bit later instead of as soon as possible). Describe why it can be advantageous. (10 p)

7. Describe how the biopharmaceuticals are produced using mammalian host cells: describe the different steps used to manufacture the biopharmaceuticals until they are ready to be delivered to the patients. Give an example of microorganism host cells used to manufacture biopharmaceuticals. Give an example of delivery device for biopharmaceutical administration. (30 p)

8. Nanoparticles for drug delivery, gene therapy and cell therapy are novel areas nowadays under investigation to generate new drugs or therapies. For these three areas, give 6 examples of therapies or drugs (already commercial or under development) as follows: at least one example of nanoparticles for drug delivery, one example of gene therapy and one example of cell therapy; and for the other three examples, the areas can be freely chosen among nanoparticles for drug delivery, gene therapy and cell therapy. For each example give a short description of the therapy. (20 p)

9. How are small molecule drugs metabolised in the liver? (10 p)

B. Questions requiring an assay-type answer, i.e. a longer answer, where you show a deeper knowledge and can analyse or reflect on the subject

10. It is recommended to read the whole question 10a-10c before starting to answer.

10a. The pharmaceutical and biopharmaceutical industry in 2016 is quite different from what it was in 1980. Between 1980 and 2016 things have changed in many different aspects with respect to the scientific knowledge, the market, the intellectual property situation, the requirements from the Authorities (e.g. FDA, EMA), etc; and many new discoveries or technologies have influenced the way new drugs are developed or produced as well as the market situation. Give at least 10 factors (or characteristics or technologies), which are different today in 2016, compared to 1980. For each factor shortly describe how the factor is different today compared to 1980 and briefly analyze how it has changed the process of drug development, the drug manufacturing or the market situation where relevant. This is a quite large question; to answer you can think about all the parts of the course. (30 p)

10b. Despite the fact that the efforts put in Research and Development (R&D) in the pharmaceutical/ biopharmaceutical industry have significantly increase since 1980, the number of new drugs registered every year (i.e. launched on the market) has not really increased. Analyze why the number of new registered drugs has not increased (between 1980 and 2016). (30 p)

10c. Given the situation in 2016 and the comparison that you have made in item 10a., in your opinion, will the number of new registered drugs increase in the next 10 years? This is an open question that has not directly been answered in the course. The motivation of your answer (using item 10a.) is therefore very important. (20 p)

11. A common way to describe the drug discovery process is to divide it into four stages: Target Identification (TI), Hit Identification (HI), Lead Identification (LI) and Lead Optimization (LO). Describe typical activities during the different stages and the deliverables of each step. (40 p)

12. Antibodies are very efficient drugs and are delivering very successful therapies.

12a. Nowadays human or humanized antibodies are used. Explain what is a humanized antibody and why humanized or human antibodies are used. (10 p)

12b. Many drugs are antibodies on the market. The field is now developing or creating many different types of new molecules, which are not only antibodies (i.e. IgG) but are derived from these. Give at least three reasons (or new opportunities) to use antibody-derived molecules instead of only IgG. (10 p)

12c. Describe at least four types of antibody-derived drugs (already registered as drugs or under development). Explain their mechanism of action and discuss why they are (or can be) better drugs than IgG only. (20 p)